Computational analysis of the contribution of ionic conductances to ECG parameters

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Abnormal heart rhythms cause 10-15% of adult deaths in the developed world. A loss of function mutation in just one of the cardiac ion channels that underlie electrical signaling in the heart is sufficient to significantly increase the risk of sudden death, and often at a young age. However, one of the problems facing cardiology is stratifying patient risk – deciding when, where and in whom these rhythm disturbances will occur. This is especially problematic since genotype—phenotype relationships for many of these disorders are so variable. For example, a particular ion channel mutant may be pathogenic in one patient and quite benign in another.

Recent genome-wide association studies (GWAS) and whole exome sequencing projects have identified hundreds of genetic variants in cardiac ion channel genes. Many of these are undoubtedly benign but many are also likely to result in small alterations of function that are able to modify the phenotypic presentation of a given mutation – so called epistatic effects. However, how can one interpret the effect of multiple small perturbations to a multivariable nonlinear dynamic system such as the electrical system of the heart? Computer simulations have provided one avenue for evaluating such phenomena at the level of the cell, but until recently, large scale simulation at the level of tissue and whole organs has been limited by the computational burden imposed by the complexity of these systems. However, massive parallelisation of simulations in line with the recent *general purpose computing on graphical processing units* paradigm (GPGPU) is allowing us to overcome this computational roadblock. As a result of these technologies, amongst others, quantitative interrogation of electrical propagation in more complex cardiac tissue arrangements is now achievable on a practical timescale.

Here, we have developed a GPGPU model of the electrocardiogram (ECG), based on the O'Hara-Rudy model of the human cardiac action potential, and used partial least squares analysis to interrogate how each of the different ion channel current components contribute to the parameters describing ECG signals. In addition to reproducing well-described relationships between repolarization durations and delayed rectifier potassium currents, our analysis can explain previously unexplained clinical observations in relation to ECG signal characteristics. These results show how emerging computational techniques can contribute to progress in clinical research and mark some of the first steps towards realizing the potential promised by organ level simulations of the heart.